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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/749,630	12/31/2003	Heinz-Werner Kleemann	DEAV2002/0095 US CNT	9797
5487	7590	01/10/2006	EXAMINER	
ROSS J. OEHLER AVENTIS PHARMACEUTICALS INC. ROUTE 202-206 MAIL CODE: D303A BRIDGEWATER, NJ 08807			SEAMAN, D MARGARET M	
			ART UNIT	PAPER NUMBER
			1625	
DATE MAILED: 01/10/2006				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/749,630	Applicant(s) KLEEMANN ET AL.	
	Examiner D. Margaret Seaman	Art Unit 1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 September 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-64 is/are pending in the application.
- 4a) Of the above claim(s) 7,21-35,37,39,41,43,45 and 47 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6,8-20,36,38,40,42,44,46 and 48-64 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This application was filed 12/31/2003 which is a CON of PCT/EP03/07024 (7/2/2003). Claims 1 – 6, 8-20, 36, 38, 40, 42, 44, 46 and 48-49 are before the examiner and claims 7, 21-35, 37, 39, 41, 43, 45 and 47 remain withdrawn.

Election/Restrictions

1. This application contains claims 7, 21-35, 37, 39, 41, 43, 45 and 47 drawn to an invention nonelected with traverse in Paper No. 5/16/2005. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.
2. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. The rejection of claims 9-20, 36, 38, 40, 42, 44, 46 and 48 and now new claims 50-64 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is upheld for reasons of record. Applicant argues that there is no requirement for the specification to have written description. The specification does not teach nor provide a nexus between modulation of the NHE-1 receptor and the **prevention** of any condition/disease. Claims drawn to "a method of treatment of a disease, by inhibiting the cellular sodium proton antiporter (Na^+/H^+ exchanger) activity of a disease, wherein the disease is selected from ... comprising administering to a patient in need thereof, an effective amount of a compound according to claim 1" and the diseases listed having a clear correlation between the activity of the compound and the treatment of the particular disease would appear to have written description. However, the instant specification does not provide a correlation between the tested activity of the compound and the specific disease

2. Claims 9-20, 36, 38, 40, 42, 44, 46 and 48 and now new claims 50-64 are (remain) rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

- 1) The breadth of the claims,
- 2) The nature of the invention,
- 3) The state of the prior art,
- 4) The level of one of ordinary skill,
- 5) The level of predictability in the art,
- 6) The amount of direction provided by the inventor,
- 7) The existence of working examples,
- 8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The nature of the invention: The nature of the invention is the method of treating or preventing a disorder that is modulated by the NHE-1 receptor.

The state of the prior art: The state of the prior art is that it involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat or prevent which specific disease). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art

would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. Drugs that are known to be effective against small cell lung cancer are inactive in melanoma (Sof'ina et al, Experimental Evaluation of Antitumor Drugs in the USA and USSR and Clinical Correlation NCI Monograph 55. NIH Publication No. 80-1933 (1980), page 77)

The predictability in the art: It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to the therapeutic effects of all diseases, whether or not the modulation of NHE-1 receptors would make a difference in the disease. Hence, in the absence of a showing of a nexus between any and all known diseases and the modulation of NHE-1 receptors, one of ordinary skill in the art is unable to fully predict possible results from the administration of the compound of claim 1 due to the unpredictability of the role of modulation of NHE-1 receptors.

The presence or absence of working examples: The compounds have been tested for inhibition of NHE-1. However, the instantly claimed compounds have not been tested for their ability to treat or prevent any specific disease/condition, including all cancers. Compound 15 has 5-position Hydrogen while compound 16 has 5-position methoxy and their activities are 0.0015 for compound 15 and 1.67 for compound 16. Compound

14 has a chlorine substituent with 2.46 activity while compound 13 has fluorine with 0.039 activity. Compound 16 has a cinnolin substituent with 1.67 activity as compared to compound 11 has quinoline substituent with 0.047 activity. Compound 5 has a 2-quinoline with 4.98 activity as compared to compound 6 having 4-quinoline with 0.206 activity. These activities show that for very small differences in structures, there are very large differences in their activities. Due to this, it is unclear as to how such activities can be linked to the treatment or prevention of diseases/conditions without being directly tested for such activity.

The amount of direction or guidance present: The guidance present in the specification is that of the compounds that any compounds having such NHE-1 inhibitory activity will treat any disease/condition that has been linked to this NHE-1 receptor. These diseases/conditions range from cytotoxic therapy to overexcitability of the CNS to high blood pressure. The specification states that NHE-1 receptors have been linked to many different activities of the body and therefore play a role in a wide variety of diseases/condition. However, there are no examples of the instantly claimed compounds (or other compounds having the same NHE-1 receptor activity) actively treating a disease/condition. The specification does not seem to enable a correlation between the mediation of NHE-1 receptors and the treatment of any and all diseases.

The breadth of the claims: The claims are drawn to the treatment and prevention of any and all diseases mediated by the NHE-1 receptor with the compound of claim 1.

The quantity of experimentation needed: The quantity of experimentation needed is undue. One skilled in the art would need to determine what diseases out of all known diseases would be benefited by the mediation of NHE-1 receptors and then would further need to determine which of the claimed compounds would provide treatment of the disease.

The level of the skill in the art: The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compounds of claim 1 for the treatment of any disease. As a result necessitating one of ordinary skill to perform an exhaustive search for which diseases can be treated by which compound of claim 1 in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, one of ordinary skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compounds of the instant claims, with no assurance of success.

This rejection can be overcome by deleting the claims.

Applicant argues that any one of ordinary skill would not have any difficulty in using the compounds of claim 1 to treat diseases/condition because such experimentation would be routine in nature. However, the identification of what diseases/condition could be treatable or preventable by the instant activity, much which diseases are treatable as compared to preventable would itself be undue experimentation. From that, what compounds encompassed by the instant claim 1 could treat or prevent a specific disease would entail undue experimentation because as stated above, prior art acknowledges that part of that undue experimentation involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat or prevent which specific disease) while there is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. Known drugs that are effective against small cell lung cancer are inactive in melanoma. This is determined through experimentation which this specification does not encompass and such experimentation

for just treating cancers is undue experimentation. Taking all of the above factors into consideration, the instant claims are not enabled by the instant specification.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

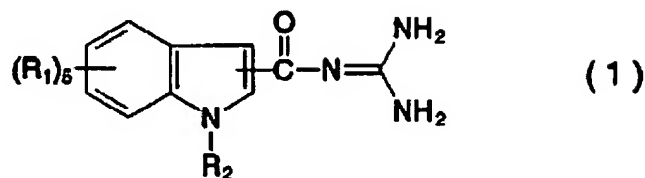
4. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. Claims 1-6, 8-20, 36, 38, 40, 42, 44, 46 and 48-49 remain and now claims 50-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0 708 091 A1.

EP teaches compounds of formula

(57) Indolylguanidine derivatives of formula (1):



and the EP defines the equivalent to the instant Ar being aromatic rings wherein the aromatic rings includes both heteroaromatic rings and non-heteroaromatic rings or aromatic rings.

The difference between the instant claims and the prior art is that there are no examples given in the EP for the aromatic ring to be a 9-10 membered bicyclic ring.

It would have been obvious to one of ordinary skill in the art to make the compounds of the EP with the equivalent to the Ar being heterocyclic bicyclic ring because the EP teaches that the R2 moiety can be heteroaromatic and has examples of the moiety being pyridine and piperidine.

Applicant argues that the motivation to change the EP equivalent of Ar from the examples aromatic ring to a different heterocyclic bicyclic ring is hindsight provided by the instant specification. However, the motivation to change an aromatic non-heterocyclic ring to an aromatic heterocyclic ring is provided by the EP with the examples of the Ar equivalent moiety being pyridine and piperidine. The prior art EP provides the motivation to change within their own teaching why to change one aromatic ring for another aromatic ring, which encompasses the instantly claimed invention. The rejection is upheld.

Conclusion


6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. Margaret Seaman whose telephone number is 571-272-0694. The examiner can normally be reached on 730am-4pm, Monday-Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecelia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


D. Margaret Seaman
Primary Examiner
Art Unit 1625

dms